REMARKS

The Claimed Invention

Claims 74, 81, 87, 93, 100-104, 106-109, 111-115 and 117-119 are pending in this application.

These claims define methods of treatment using one of two compounds or their pharmaceutically acceptable salts. A salt of one of these compounds, *N*-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea (entry 42 in the specification) is the active ingredient in the drug Nexavar®, referred to as Sorafenib and BAY 43-9006 prior to market approval. The other compound, *N*-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(carbamoyl)-4-pyridyloxy) phenyl) urea (entry 43 in the specification) is a derivative thereof and is also a raf kinase inhibitor.

Claim 117 defines a method for inhibiting raf-kinase in a human or mammal by administering one of these two compounds. It does not require the treatment of a disease such as cancer in a human or mammal. It only requires that the inhibition of raf kinase within the human or mammal be effected.

Claims 74 and 106 define methods for using one of these two compounds to treat a solid cancer. Claim 106 specifies the tosylate salt of these compounds is used.

Claims 81 and 107 define methods for using one of these two compounds to treat a carcinoma, myeloid disorder or adenoma. Claim 107 specifies the tosylate salt of these compounds is used.

Claims 87 and 108 define methods for using one of these two compounds to treat a carcinoma of the lung, pancreas, thyroid, bladder or colon. Claim 108 specifies the tosylate salt of these compounds is used.

Claims 100, 101, 102, 103, 104, 109, 110, 112, 113, 114, 115, 118 and 119 define methods for using one of these two compounds to treat a specific which is carcinoma of the lung, pancreas, thyroid, bladder or colon in a human in need thereof.

Rejection under 35 U.S.C. §112, first paragraph

Claims 74, 81, 87, 93, 100-103, 106-108, 110-114 and 117 stand rejected under 35 U.S.C. §112, first paragraph.

As discussed above, one of the two compounds used in the methods defined by these claims is the active agent in Nexavar®, which has been approved for the treatment of renal cell carcinoma (RCC) in more than 70 countries and hepatocellular carcinoma (HCC) in more than 40 countries. It has been reported that there are over 230 clinical trials ongoing with Nexavar. See www.clinicaltrials.gov.
It has also been reported that Nexavar® has been studied in more than 20 tumor types and in nearly 8000 clinical trial patients. www.medicalnewstoday.com/articles/42734.php, including lung, thyroid, gastric and ovarian cancers, as shown by the publications made of record earlier and discussed below.

Awada et al., Br J Cancer. 2005 May 23;92(10):1855-61, treated patients with different solid tumors which included the following types colon, breast, kidney, ovary, liver, gastrointestinal, head and neck, lung, melanoma and others. The drug was administered orally at various dosage levels and frequency. The administration of BAY 43-9006 was consistent with the teachings of the disclosure of the application, which illustrates undue experimentation was not necessary to perform the treatment methods claimed herein.

Clark et al, Clinical Cancer Res.2005 Aug 1,11(15):5472-80, orally administered BAY 43-9006 at escalated dosages to patients with solid tumors, the primary tumor sites in these patients were the colon, sigmoid, pancreas abdomen and others/unknown. The use of BAY 43-9006 was consistent with the teachings of this application.

Moore et al., Ann Oncol. 2005 Oct; 16 (10):1688-94.Epub 2005 Jul 8, orally administered BAY 43-9006 to patients having advanced refractory solid tumors with the following primary tumor types: colon, ovary, peritoneum, pancreas, kidney, cervix, breast and pharynx. The dosage levels and frequency were varied during the trial and were consistent with the teachings of this application.

Escudier et al, N Engl J Med 2007 Jan 11, 356 (2):125-34, administered oral sorafenib (at a dose of 400 mg twice daily) to patients with renal cell carcinoma consistent with the teachings of this application.

The approved use of Nexavar and the methods employed in the studies above are consistent with the teachings of the disclosure of this invention. No evidence has been presented that any experimentation was necessary to treat the various solid tumors identified in these references and the patient class for these clinical trials was

not limited colon cancer, which the examiner alleges is the only condition for which the specification is enabling.

Theses studies endorse the teachings in the specification and demonstrate the claimed methods are enabled by the specification. The dosages, modes of administration and patient classes used in these studies are consistent with the teachings in this specification. No evidence has been presented to question the teachings within the specification to support the rejection.

Applicants rely on the state of the art references (Monia, Kolch, Daum et al. and Fridman et al) to show the correlation between the inhibition of raf kinase with the inhibition of the growth of a variety of solid tumor types (Monia et al.), the blocking cell proliferation (Kolch et al.) and the reversion of transformed cells to the normal growth phenotype (Daum et al., Fridman et al). The disclosure in the specification provides the details necessary to establish therapeutic treatments with the compounds disclosed therein. The adequacy of this disclosure is confirmed by the studies discusses above and others made of record in the IDS filed on June 29 2007. Where Monia, Kolch, Daum et al. and Fridman et al are speculative, the disclosure of this application is specific in describing active compounds and methods for using them.

The Examiner finds "The re is no evidence of record that the claimed compounds are actually efficacious in treating all types of solid tumor, carcinoma, myeloid disorders or adenoma or inhibit RAF–kinase generally." This is clearly not true in view of the numerous studies made of record. The drug Nexavar has been administered in thousands of patients and efficacy has been confirmed in that Nexavar has been approved for the treatment of renal cell carcinoma (RCC) in more than 70 countries and hepatocellular carcinoma (HCC) in more than 40 countries. Nexavar was the first drug approved for use in treating renal cell carcinoma (RCC), such that the drugs efficacious properties are not only real, they are unique. As mentioned above, it is reported that over 230 clinical trials are using Nexavar.

It is alleged the references relied on to show the state of the art (Monia, Kolch, Daum et al. and Fridman et al) invite further research into the treatment of solid tumor, carcinoma, myeloid disorder, adenoma etc, through the inhibition of raf kinase. No evidence ahs been presented to support this allegation. If true, this invitation for further research was meet by the applicants in identifying potent raf kinase inhibitors.

The correlation between the inhibition of raf kinase and treating various cancers was not in question at the time of the invention.

The examiner alleges the guidance provided in the specification is "limited to an in vitro cell proliferation assay showing inhibition of two colon cancer cell lines and summary instructions relating to an in vivo assay in mice that can be performed to determine the inhibition of a human Aden carcinoma cell line." As argued previously, this ignores the results of the assay for raf kinase inhibition and the state of knowledge of those skilled in the art (Monia, Kolch, Daum et al. and Fridman et al) correlating such activity with treating tumors. For example, Monia et al state at p.673, col. 2, lines 17-21:

> The recent discovery that raf kinases function in part as downstream mediators of ras oncogene action suggests that inhibitors of raf gene expression may prove useful in the treatment of ras-dependent tumors.

Applicants clearly provide sufficient guidance to make the two compounds recited in the claims as described on page 66, prepare and administer pharmaceutical compositions with these compounds in the treatment of cancers as described on pages 10-14, and, although not necessary, they also show they are efficacious in the assays described on pages 94-96. The examiner has not provided any evidence it would not be routine to use these compounds in the treatment of cancer. The numerous studies made of record demonstrate that it is routine to do so. No evidence has been presented that any of these studies varied from the teachings within this disclosure.

To the extent the disclosure does not provide specific dosages for a given treatment, it would at most involve routine experimentation, if any at all, for one skilled in the art to treat any one of the recited cancers with the compounds of this invention. The enablement requirement is satisfied if, "the specification teaches those in the art enough that they can make and use the claimed invention without "undue experimentation" See, *Amgen Inc. v. Hoechst Marion Roussel,* 314 F.2d 1313, 65 USPQ 2nd 1385 (Fed Cir. 2003). Using the claimed compounds would be routine for those skilled in the art in view of Applicant's disclosure, as is shown by the various studies made of record.

The Examiner has indicated the reasons for the rejection in the office action of September 24, 2007 are repeated. In the last office action, the teachings in the

specification were found to be insufficient, requiring that the state of the art must clearly correlate the assays employed in the specification and clinical efficacy for treatment of the claimed diseases. Such a showing is unnecessary since there is no evidence that the results of the assay are inaccurate or are not reasonably correlated with efficacy. The numerous studies showing the efficaciousness of Nexavar is consistent with the absence of evidence to the contrary. Furthermore, applicants did provide indirect evidence in a paper by Monia presented in 1997 with data showing that the raf kinase inhibitor ISIS 5132 exhibited anti-tumor activity in varying tumor types such as lung, prostate, bladder, breast, melanoma and colon.

Applicants maintain that the express disclosure within the specification is sufficient to enable all of the claims herein and that further assays or data to support the methods of treatment are not necessary. Based on the teachings within the art of the broad spectrum of activity of raf kinase inhibitors, one skilled in the art would recognize that the compounds recited in the claims herein having raf kinase activity would be effective in treating the diseases claimed.

Claims 87, 93, 100-103,108, 109 and 111-114

Claims 87, 93, 100-103,108, 109 and 111-114, name the following specific cancer types: lung, pancreas, thyroid, bladder and myeloid leukemia. There is no evidence to a) doubt these claims are enabled by the disclosure within the specification or b) support the rejection of these claims under 35 USC §112 first paragraph, particularly in view of the state of the art which had correlated raf kinase activity with the treatment of various cancers including lung and bladder cancer (Monia), as well as pancreatic cancer and colon cancer (Fridman).

The specification expressly teaches the compounds disclosed are suitable for the treatment of these cancers and there is no reason to doubt the general and specific disclosures therein regarding the treatment of solid tumors such as these. In addition, studies of record have confirmed the compound Nexavar is efficacious in treating colon cancer (Awada et al, Clark et al, Moore et al), lung cancer (Awada et al.), pancreatic cancer (Clark et al and Moore et al.) and myeloid leukemia (Éclair, et al., "96th Annual Meeting, Anaheim/Orange County, CA, April 16-20, 2005). Furthermore, there are ongoing trials where Nexavar is being used to treat thyroid cancer (ClinicalTrials.gov id: NCT00654238, Sponsor: University of Pennsylvania)

and bladder cancer. (ClinicalTrials.gov id: NCT00112905, Sponsor: Eastern Cooperative Oncology Group; ClinicalTrials.gov id: NCT00112671, Sponsor Princess Margaret Hospital, Canada).

In the view of the lack of evidence to support the allegation that these claims are not enabled and the extensive research which confirms the teachings within the disclosure are true, the methods of Claims 87, 93, 100-103,108, 109 and 111-114 are clearly enabled by the specification and the rejection of these claims under 35 USC §112 first paragraph, should be withdrawn.

Claims to treating carcinoma of the colon

Applicants acknowledge that claims 104, 115, 118 and 119 directed to treating carcinoma of the colon have been found to satisfy 35 USC §112, first paragraph. Given the scope of the disclosure provided, including the enabling disclosure for treating carcinoma of the colon, it would at most involve routine experimentation, if any at all, for one of ordinary skill in the art to treat other solid tumors with one of the two compounds named. Explicitly providing dedicated assays for each form of cancer is not necessary to enable the methods claimed. See, for example, *In re Howarth,* 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art.)

Claim 117

Claim 117 is directed to a method of inhibiting raf -kinase in a human or other mammal with one of the two compounds listed. No reasons have been given for rejecting this claim as not enabled. It is not a method of treatment claim for any condition, including cancer, so the issues raised by the examiner regarding the complexities in treating cancer are moot.

The specification provides sufficient guidance to prepare the two urea compounds and also provides sufficient guidance on how to prepare and administer compositions with these compounds, including dosages. The specification also shows that the free base of these compounds, compounds 42 and 43, inhibit raf kinase in the assays disclosed.

The examiner has not identified any element of the claim for which the disclosure is allegedly deficient and has not identified any claim term, which is allegedly indefinite. Instead, the examiner reads limitations into the claim regarding

the treatment of diseases. There is no basis for incorporating treatment limitations into the claim, which is improper, (*See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313, 75 USPQ2d 1321, 1326 (Fed. Cir. 2005) (en banc), MPEP 2111.01, and *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989)).

In that there is no basis for referring to the specification for the meaning of any claim term and there clearly is no basis for reading treatment limitations into the claim, the rejection of claim 117 should be withdrawn.

The claim is not a reach through claim in that the agents used are defined by structure(chemical name) and not by function. As such, the claim does not encompass the use of unforeseen or unknown compounds. In that the claim does not encompass unknown subject matter, the requirements of 35 USC§ 112, first and second paragraphs are met.

To the extent new methods of treatment using the two named compounds would infringe these claims; these new methods would also infringe composition claims to the two compounds. If claim 117 is a reach-through claim then all composition claims are reach through claims.

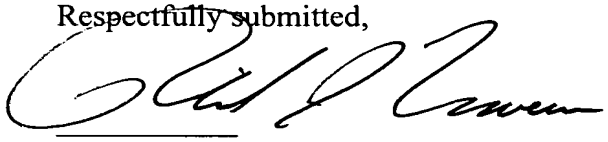
For the reasons indicated above, Applicants maintain that they have provided more than adequate guidance and examples to enable the claimed invention and submit all claims meet the requirements of 35 U.S.C. §112, first and second paragraphs.

Double Patenting

Claims 74, 81, 87, 93, 99-104 106-115 and 117-119 have been rejected under the doctrine of obviousness type double patenting over claims 38, 89-91 and 121 in US Serial No. 10/042,226. As indicated in the previous response, applicants will address this rejection when the claims herein are otherwise allowable.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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